Measles outbreak in 31 schools: risk factors for vaccine failure and evaluation of a selective revaccination strategy

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Objective: To examine the risk factors for measles vaccine failure and to evaluate the effectiveness of a selective revaccination strategy during a measles outbreak.
Design: Matched case–control study.
Setting: Thirty-one schools in Mississauga, Ont.
Subjects: Eighty-seven previously vaccinated school-aged children with measles that met the Advisory Committee on Epidemiology's clinical case definition for measles. Two previously vaccinated control subjects were randomly selected for each case subject from the same homeroom class.
Interventions: All susceptible contacts were vaccinated, and contacts who had been vaccinated before Jan. 1, 1980, were revaccinated. When two or more cases occurred in a school all children vaccinated before 1980 were revaccinated.
Main outcome measures: Risk of measles associated with age at vaccination, time since vaccination, vaccination before 1980 and revaccination.
Results: Subjects vaccinated before 12 months of age were at greater risk of measles than those vaccinated later (adjusted odds ratio [OR] 7.7, 95% confidence interval [CI] 1.6 to 38.3; $p = 0.01$). Those vaccinated between 12 and 14 months of age were at no greater risk than those vaccinated at 15 months or over. Subjects vaccinated before 1980 were at greater risk than those vaccinated after 1980 (adjusted OR 14.5, 95% CI 1.5 to 135.6). Time since vaccination was not a risk factor. Revaccination was effective in reducing the risk of measles in both subjects vaccinated before 1980 and those vaccinated after 1980 (adjusted OR reduced to 0.6 [95% CI 0.1 to 5.3] and 0.3 [95% CI 0.13 to 2.6] respectively). However, only 18 cases were estimated to have been prevented by this strategy.
Conclusions: Adherence to routine measles vaccination for all eligible children is important in ensuring appropriate coverage with a single dose. The selective revaccination strategy's high labour intensiveness and low measles prevention rate during the outbreak bring into question the effectiveness of such a strategy.

Objectif : Examiner les facteurs de risque liés à un échec du vaccin antirougeoleux et évaluer l'efficacité d'une stratégie de revaccination sélective au cours d'une poussée de rougeole.
Conception : Étude de cas–témoins jumelés.
Contexte : Trente et une écoles de Mississauga (Ont.).
Objet : Quatre-vingt sept enfants d'âge scolaire atteints de la rougeole malgré une vacination antérieure et satisfaisant à la définition d'un cas clinique de rougeole du Comité consultatif de l'épidémiologie. On a choisi au hasard, pour chaque cas, deux sujets témoins antérieurement vaccinés provenant de la même classe-foyer.

Interventions : Tous les contacts possibles ont été vaccinés et les contacts qui avaient été vaccinés avant le 1er janvier 1980 ont été revaccinés. Dans les écoles où deux cas ou plus ont été signalés, tous les enfants vaccinés avant 1980 ont été revaccinés.

Principales mesures de résultats : Risque de contracter la rougeole, en fonction de l'âge au moment de la vaccination, du temps écoulé depuis la vaccination, du fait que la vaccination soit antérieure à 1980, et de la revaccination.

Résultats : Les sujets vaccinés avant l'âge de 12 mois risquaient plus d'être atteints de la rougeole que les sujets vaccinés plus tard (risque relatif [RR] rajusté de 7,7, intervalle de confiance [IC] à 95 % de 1,6 à 38,3 $p = 0,01$). Les sujets vaccinés entre l'âge de 12 et 14 mois n'étaient pas plus à risque que les sujets vaccinés à l'âge de 15 mois ou plus. Les sujets vaccinés avant 1980 étaient plus à risque que les sujets vaccinés après 1980 (RR rajusté de 14,5, IC à 95 % de 1,5 à 135,6). Le temps écoulé depuis la vaccination n'était pas un facteur de risque. La revaccination a réduit le risque de rougeole à la fois chez les sujets vaccinés avant 1980 et chez ceux qui l'ont été après 1980 (RR rajusté ramené à 0,6 [IC à 95 % de 0,1 à 5,3] et 0,3 [IC à 95 % de 0,13 à 2,6] respectivement). On estime toutefois que cette stratégie n'a permis de prévenir que 18 cas.

Conclusions : Il importe de continuer de vacciner régulièrement contre la rougeole tous les enfants admissibles afin de bien les protéger à l'aide d'une seule dose. Comme la stratégie de revaccination sélective consomme beaucoup de main-d'oeuvre et comme le taux de prévention de la rougeole est faible en cas de poussée, l'efficacité d'une telle stratégie est remise en question.

Elimination of measles was strongly advocated during the 1980s in Canada.[1,2] From 1981 to 1989 incidence rates were under 17 per 100 000 population except for outbreaks in 1986 and 1989, when the national rates were 59.1 and 42.5 per 100 000 respectively.[3,4] In Ontario from September 1989 to September 1992 over 8500 cases were reported, for an average annual incidence rate of 42 per 100 000 (Monika Naus, Ontario Ministry of Health, Toronto: personal communication, 1993).

The National Advisory Committee on Immunization (NACI) recommends that all children be vaccinated against measles on or as soon as possible after their first birthday and that in an outbreak all contacts and their siblings who have no proof of immunity or were vaccinated before Jan. 1, 1980, be vaccinated immediately unless valid contraindications exist.[1,5] The recommendation of a selective revaccination strategy in Canada has been controversial because the rationale was based on US reports that suggested children vaccinated before 1980 are at increased risk of measles.[6,7] The intensive resources required to implement such a strategy has led to resistance among public health departments. Ontario was the only province that attempted to implement such a strategy during outbreaks.

In recent years case–control and retrospective cohort studies, mostly from the United States, have reported risk factors for measles vaccine failure. The age at vaccination, especially before 12 months of age, has been a strong risk factor.[8-10] Moreover, some studies have shown that vaccination between 12 and 14 months is associated with a higher rate of vaccine failure than vaccination at 15 months of age or more.[6,8,9,11-13] The lack of provider-verified vaccination records was found to occur more commonly in measles cases than in nonmeasles cases in some studies.[6,11-14] Vaccination before 1980 and

waning immunity have also been reported as risk factors.[6,7]

In September 1990 a measles outbreak in an Ontario health unit provided an opportunity to conduct a study to investigate two issues: (a) the risk factors for vaccine failure during measles outbreaks and (b) the effectiveness of a selective revaccination strategy in controlling measles outbreaks.

With 31 schools involved in the outbreak and small attack rates per school, a case–control study was more feasible than a retrospective cohort study. The latter design would have required the follow-up of thousands of students in many schools.

Background information

Mississauga, just west of metropolitan Toronto, had a population of 450 000 in 1990, and 128 elementary and 27 secondary schools. School-aged children between 5 and 19 years of age constituted 22% (99 457) of the population. Since 1982 the Ontario Immunization of School Pupils Act[15] has required that all children provide proof of immunity against measles and other diseases preventable by vaccine or face suspension from school. Proof of immunity is the receipt of measles vaccine on or after the first birthday, documentation of measles diagnosed by a physician or serologic evidence of immunity. Only medical or philosophic exemptions are permitted under the act.

Outbreak control measures included contact tracing, vaccination of susceptible contacts and revaccination of contacts vaccinated before Jan. 1, 1980. When two or more cases occurred at a school all the students vaccinated before 1980 were revaccinated. Students who could not or would not be vaccinated were excluded from school until 2 weeks after the onset of the last case

in the school. Revaccination was not generally recommended for people vaccinated after 1980; however, some parents sought revaccination for these children from their physicians.

Methods

A case–control study was conducted in which each subject with measles reported between Sept. 1 and Dec. 31, 1990, to the Peel Regional Health Unit was matched to two control subjects randomly selected from the same classroom. Selection of control subjects who shared the same air space in the classroom as the case subjects ensured equivalent risk of measles exposure between the two groups.

Case subjects

Case subjects had to meet the clinical case definition for measles of the Advisory Committee on Epidemiology:[5] temperature of 38.3°C or greater and cough, coryza or conjunctivitis followed by generalized maculopapular rash for at least 3 days. The confirmed case definition required the presence of one of the following: (a) measles virus isolated in specimens, (b) a fourfold rise in the serum antibody titre, (c) the presence of measles-specific IgM or (d) clinically suspected measles in a person known to be a contact of a person with laboratory-confirmed measles.[5] Case subjects were excluded from the study if they (a) had never received measles vaccine, (b) were vaccinated with more than one dose of measles vaccine before Sept. 1, 1990, or (c) did not attend school in Mississauga.

Information was gathered from parents and physicians over the telephone by public health nurses during the initial management phase of the outbreak. Parents or physicians were contacted later by the investigator to verify the day, month and year of vaccination in written records. Vaccination records were defined as nonverifiable if no written documentation of a vaccination date was available and incomplete if the full date was unavailable.

Control subjects

Randomly allocated numbers were used to select two control subjects per case subject from homeroom class lists. Similar exclusion criteria were applied, with the following additions: (a) documented history of measles, (b) signs and symptoms that met the clinical or confirmed case definition for measles during the outbreak or (c) absence from class during the entire infectious period of the matched case subject.

Information was gathered with a standard questionnaire mailed to the parents and returned in a self-addressed, stamped envelope. The first reminder was sent 3 to 4 weeks after the questionnaire had been mailed; a second reminder was sent if no response was received after another 3 to 4 weeks. Vaccination dates were verified in the same manner as with case subjects.

Dependent and independent variables

The outcome of interest was the presence or absence of measles that met the clinical case definition. The independent variables of interest were defined as follows.

• Age at vaccination: the number of months between the date of birth and the date of vaccination, examined both as a categoric variable (less than 12 months, 12 to 14 months, 15 or more months) and as a continuous variable.

• Time since vaccination: the number of years from the date of vaccination until the date of disease onset in the case subject, examined as a categoric variable (less than 5 years, 5 to 9 years, 10 or more years) and as a continuous variable.

• Verifiability of vaccination records: a dichotomous variable for which the ability to confirm vaccination dates was used to classify subjects.

• Vaccination before or after 1980: a dichotomous variable defined as the receipt of measles vaccine before or after Jan. 1, 1980.

• Revaccination during the outbreak: a dichotomous variable for which the receipt of measles vaccine before disease onset was used to classify subjects.

Sample size

Sample size was calculated on the basis of measles vaccination frequency of 48% at 12 to 14 months, measles risk of 6.2 (95% CI 4.0 to 9.9) if vaccination occurred at 12 to 14 months, two-sided α value of 5% and a power of 90%. The frequency of vaccination was obtained from an analysis of 10 391 randomly chosen student vaccination records from the Ontario Ministry of Health. Measles risk was estimated from a meta-analysis of published studies.[6,8,11] To detect an odds ratio between 2 and 7 in a 2:1 matched case–control study, sample sizes of 24 to 148 are required.[16]

Statistical analysis

Conditional logistic regression with maximum likelihood estimation of regression coefficients was used in the multivariate analysis.[17]

Results

Between Sept. 1 and Dec. 31, 1990, 132 cases of measles were reported to the health department (Fig. 1); 126 met the clinical case definition, and 61 (48.4%) of these cases were serologically confirmed. Sixty-nine (54.8%) of the subjects were male. Immunization status was verifiable in 106 (84.1%) cases.

The index case subject, whose disease was serologically confirmed, was a 17-year-old student who had received measles–rubella vaccine at 5 months of age. The source of infection was unknown. The disease spread from this student to a 15-year-old cousin in the same school. Nineteen cases in three generations occurred at the index school.

The mean age of the case subjects was 11.6 years (range 11 months to 37 years). The age-specific incidence rate was highest among children 10 to 14 years of age (147.5 per 100 000); the next highest rates were among children 15 to 19 years (74.8 per 100 000) and those 5 to 9 years (71.6 per 100 000). In all, 101 (80.2%) of the 126 case subjects had been vaccinated; however, for 17 (13.5%) vaccination was before the age of 12 months. Of the 99 case subjects for whom the year of vaccination was available, 54 were vaccinated before and 45 after Jan. 1, 1980.

Complications of measles were reported in 29 (23.0%) of the cases: otitis media in 12 (9.5%), pneumonia in 7 (5.6%), bronchitis in 5 (4.0%), and fever, dehydration and cough in 5 (4.0%). In six of these cases admission to hospital was required, but no deaths occurred. The nonvaccinated and vaccinated groups did not differ in terms of types of complications. However, significantly more of the subjects in hospital than of those not in hospital were nonvaccinated (4/6 v. 4/23, $p = 0.03$, Fisher's exact test).

Of the 126 cases 102 (81.0%) occurred in 31 schools. Vaccination coverage rates in these schools ranged from 69% to 98% (median 94%). Attack rates were less than 1% in 90% of the schools. Twenty schools had 1 reported case, eight had 2 to 9 cases, and three had 11 to 19 cases. There was no correlation between the attack rates and the coverage rates in the schools. Despite revaccination clinics at 10 schools, 53 (42.1%) cases occurred before these clinics could take place.

Of the 126 cases 42 (33.3%) met the Advisory Committee on Epidemiology's definition of a pre-

ventable case.[5] In 17 (40.5%) vaccination had occurred before 12 months of age, in 15 (35.7%) the subjects were over 13 months of age and had not been vaccinated, and in 10 (23.8%) they were over 12 months of age with no documented receipt of live measles vaccine.

Case–control study

Of the 126 case subjects 87 were included in the case–control study after application of the exclusion criteria. Of the remaining 39 subjects 24 were not students, 13 had not been vaccinated, and 2 had received two doses of measles vaccine. Vaccination records were verifiable for 81 (93.1%) of the eligible case subjects.

The questionnaire was returned by 161 (89.4%) of the control subjects selected. A total of 26 were excluded: 9 had been vaccinated twice, 8 had not been vaccinated, 5 met the clinical case definition for measles, and 4 were matched to case subjects excluded from the study. Vaccination records were verifiable for 122 (90.4%) of the eligible control subjects.

The characteristics of the subjects are described in Table 1. The students in the case group were more likely than those in the control group to have been vaccinated before 1980 (55.2% v. 40.7%, $p = 0.05$) and before 12 months of age (21.2% v. 2.9%, $p < 0.01$). In contrast, the control subjects were more likely to have been revaccinated during the outbreak (33.6% v. 10.3%, $p < 0.01$).

The multivariate logistic regression model showed an inverse relation between age at vaccination and risk of measles (Table 2). The students at greatest risk during the outbreak were those who had been vaccinated under 12 months of age. Those vaccinated between 12 and 14 months of age were at no significantly greater risk than those vaccinated at 15 months or later.

Duration of vaccination was not found to be a significant risk factor in the analysis. The verifiability of records was not assessed, since this variable did not differ significantly between the two groups.

Of the subjects who were previously vaccinated with a single dose of vaccine, those who had been vaccinated before 1980 were at greater risk than those who had been vaccinated after 1980 (Table 3). However, receipt of a second dose (revaccination) appeared to be effective in reducing the risk in both groups.

Discussion

In this study the equivalence of exposure to measles between the case and control groups was controlled with the selection of case and control subjects from the same classrooms. The high proportion of verifiable vaccination records, the high response rate and the low frequency of missing values reduced the risk of information bias. Despite these strengths, selection bias could still have been introduced, since only reported cases from September to December 1990 were included and the out-
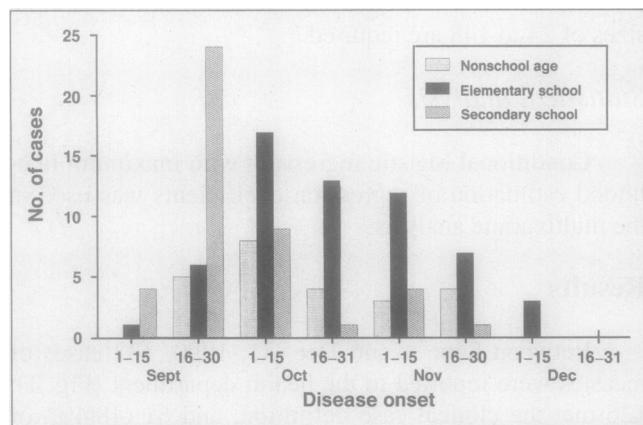
Fig. 1: Number of cases of measles reported during an outbreak in Mississauga, Ont., from Sept. 1 to Dec. 31, 1990.

break was not over until the end of May 1991.

The proportion of inadequately vaccinated individuals in this outbreak was 33.3%, as compared with 17.6% in another outbreak in Ontario.[18] The significant risk this poses emphasizes the importance of ensuring adequate measles vaccination of all nonvaccinated children 12 months of age and older and revaccination of all those vaccinated before 12 months of age.

Children vaccinated between 12 and 14 months demonstrated no significant risk for measles in the study. This may have been because the power to detect this level of risk was only 50% with 44 discordant pairs in the analysis;[19] if greater study power were present this variable may have been found to be significant, as reported elsewhere.[6,8,9,11] The other explanation is that these children may in fact not be at increased risk,[7,10,20] possibly because many were born during the 1970s and 1980s, when mothers were more likely to have vaccine immunity rather than natural immunity from measles. It has been suggested that infants of mothers who have vaccine immunity acquire lower levels of antibody at birth and lose antibody at an earlier age than infants of mothers with natural immunity and thus have a reduced possibility of interference from live measles vaccine.[21] Waning immunity and the nonverifiability of the vaccination records were not significant risk factors in this outbreak.

Subjects vaccinated before 1980 were at greater risk than those vaccinated after 1980. This could have been because of a higher rate of primary vaccine failure before the addition of an improved heat stabilizer to the measles vaccine in 1980 or because of poorer vaccine handling practices before 1980. In this outbreak the case subjects were more likely than the control subjects to have been vaccinated not only before 1980 but also before 12 months of age. These two risk factors were present in the index case subject, and both contributed to the spread of measles in this outbreak.

Revaccination significantly reduced the risk of measles among subjects who had been vaccinated before 1980. It also appeared to reduce the risk among those who had been vaccinated after 1980. The lack of a statistically significant decline in this group was likely due to low study power. However, despite the protective effect of revaccination, the actual number of cases prevented by this strategy was relatively small. If one assumed that the ratio of case subjects vaccinated before 1980 to those vaccinated after 1980 were maintained after the revaccination period, one would have expected 25 cases of measles in people vaccinated before 1980. In fact, only seven such cases were reported. Thus, the targeted revaccination strategy may have prevented 18 cases.

The implementation of the revaccination strategy during this outbreak was extremely labour intensive: it involved the review of all vaccination records in each school, the distribution and collection of consent letters

Table 2: Effect of age at vaccination on risk of measles

Age at vaccination, mo	Adjusted OR (and 95% CI)*	p value
< 12	7.7 (1.6–38.3)	0.01
12–14	1.7 (0.8–3.4)	0.14
≥ 15	1.0 (–)	–

*OR = odds ratio, CI = confidence interval.

Table 3: Effect of one and two doses of vaccine on risk of measles during measles outbreak

Variable	Adjusted OR (and 95% CI)
One dose	
Before 1980	14.5 (1.5–135.6)
After 1980	1.0 (–)
Two doses	
First dose before 1980	0.6 (0.06–5.3)
First dose after 1980	0.3 (0.13–2.6)

Table 1: Characteristics of case and control subjects during a measles outbreak in schools in Mississauga, Ont., from Sept. 1 to Dec. 31, 1990

Characteristic	Case subjects (n = 87)	Control subjects (n = 135)
Male:female ratio	1.4	0.9
Mean age (and standard deviation [SD]), yr	11.8 (3.9)	11.5 (4.0)
Subjects whose vaccination date could be verified from records, %	93.1	90.4
Subjects vaccinated before 1980	55.2	40.7
Mean age at vaccination (and SD), yr	1.4 (1.1)	2.6 (3.0)
Subjects vaccinated before 12 mo, %	21.2	2.9
Subjects revaccinated during outbreak, %	10.3	33.6

to approximately 8500 parents of children who had been vaccinated before 1980 and the provision of 10 school-based revaccination clinics. Only in four schools was it possible to hold revaccination clinics after only two reported cases. In the other six schools the bulk of cases occurred before the revaccination clinics could take place. Even though a second dose of vaccine is protective, the difficulty in ensuring rapid revaccination of people at risk and the substantial effort associated with preventing each case brings into question the feasibility of such a strategy.[22] The US Immunization Practices Advisory Committee has instead recommended a routine two-dose measles vaccination strategy for all children.[23]

In conclusion, the findings from this study emphasize the importance of ensuring adequate one-dose measles vaccination for all children. Although a selective revaccination strategy is of limited effectiveness during an outbreak, a second dose of vaccine may further reduce the risk of measles.

I thank the late Dr. Randy Coates for his critical review of the study and the staff at the Peel Regional Health Unit for their assistance with the data collection.

References

1. Statement on recommended use of measles vaccine in Canada. *Can Dis Wkly Rep* 1990; 16: 7–10

2. Measles in Canada. *Can Dis Wkly Rep* 1989; 15: 1–7

3. Measles in Canada–1988. *Can Dis Wkly Rep* 1990; 16: 1–6

4. Measles in Canada–1989. Ibid: 213–218

5. Guidelines for measles control in Canada. *Can Dis Wkly Rep* 1991; 17: 35–40

6. Mast EE, Berg JL, Hanrahan LP et al: Risk factors for measles in a previously vaccinated population and cost-effectiveness of revaccination strategies. *JAMA* 1990; 264: 2529–2533

7. Hutchins SS, Markowitz LE, Mead P et al: A school-based measles outbreak: the effect of a selective revaccination policy and risk factors for vaccine failure. *Am J Epidemiol* 1990; 132: 157–168

8. Chen RT, Goldbaum GM, Wassilak LE et al: An explosive point-source measles outbreak in a highly vaccinated population. *Am J Epidemiol* 1989; 129: 173–182

9. Hersh BS, Markowitz LE, Hoffman RE et al: A measles oubreak at a college with a prematriculation immunization requirement. *Am J Public Health* 1991; 81: 360–364

10. Nkowane BM, Bart SW, Orenstein WA et al: Measles outbreak in a vaccinated school population: epidemiology, chains of transmission and the role of vaccine failure. *Am J Public Health* 1987; 77: 434–438

11. Shelton JD, Jacobson JE, Orenstein WA et al: Measles vaccine efficacy: influence of age at vaccination vs. duration of time since revaccination. *Pediatrics* 1978; 62: 961–964

12. Hull HF, Montes JM, Hays PC et al: Risk factors for measles vaccine failure among immunized students. *Pediatrics* 1985; 76: 518–523

13. Orenstein WA, Markowitz L, Preblud SR et al: Appropriate age for measles vaccination in the United States. *Dev Biol Stand* 1986; 65: 13–21

14. Wassilak SGF, Orenstein WA, Strickland PL et al: Continuing measles transmission in students despite a school-based outbreak control program. *Am J Epidemiol* 1985; 122: 208–217

15. The Ontario Immunization of School Pupils Act, SO 1982, c 41

16. Lui KJ: Estimation of sample sizes in case–control studies with multiple controls per case. *Am J Epidemiol* 1988; 127: 1064–1070

17. Breslow NE, Day NE: *Statistical Methods in Cancer Research*, vols 1 and 2, International Agency for Reseach on Cancer, Lyons, France, 1980

18. Measles epidemic in Waterloo region, Ontario, 1990–1991. *Can Dis Wkly Rep* 1991; 17: 219–224

19. Schlesselman JJ: *Case–Control Studies: Design, Conduct, Analysis*, Oxford U Pr, New York, 1982: 162

20. Davis RM, Whitman ED, Orenstein WA et al: A persistent outbreak of measles despite appropriate prevention and control measures. *Am J Epidemiol* 1987; 126: 438–449

21. Markowitz L, Orenstein WA: Measles vaccine. *Pediatr Clin North Am* 1990; 37: 603–625

22. Osterman JW, Melnychuk D: Revaccination of children during school-based measles outbreaks: potential impact of a new policy recommendation. *Can Med Assoc J* 1992; 146: 929–936

23. Measles prevention. *MMWR* 1989; 38 (S-9): 1–18